A Radical FLP Approach to C-C coupling

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Melen and co-workers report the reactivity of diaryl-substituted esters with $R_3P/B(C_6F_5)_3$ frustrated Lewis pairs (FLPs). Although ester C-O activation occurs for all FLP systems, use of Mes_3P induces single-electron transfer to generate a $[Mes_3P]^{+\cdot}/[C(H)Ar_2]^{\cdot}$ radical ion pair. In the presence of olefins, this reactivity is harnessed in an sp^2-sp^3 C–C heterocoupling reaction to generate α,β-substituted olefins.

Organic boron and phosphorus compounds are some the best established in the armoury of main group reagents, with provenances that can be traced to the earliest days of organoelement chemistry. Although manipulation of the π-acidic properties of phosphine (R_3P) donor ligands has long provided a focal point in both transition metal coordination chemistry and catalysis, the emergence of the frustrated Lewis pair (FLP) concept in 2006 provided Lewis acidic trialkyl- or triarylboranes with a similarly transformative shot-in-the-arm.[1] Stephan's initial discovery that an ambiphilic phosphinoborane, 4-$(Mes_2P)C_6F_4\{B(C_6F_5)_2\}$, could effect the mild and reversible heterolytic activation of dihydrogen (i.e. effective cleavage of the H-H bond into H^+ and H^-) foreshadowed an explosion of interest in the broader cooperative reactivity engendered through appropriate p-block-centred Lewis acid/Lewis base combinations.[2]

While the resultant body of research has provided a plethora of transition metal-free catalyses and bond activation processes, implicit in Stephan's initial report of H_2 heterolysis was an assumption that all this chemistry ensues through two-electron transfer and the exclusive intermediacy of diamagnetic, even electron intermediates.[3-6] Although this viewpoint continued to prevail for the entirety of the subsequent decade, the concentrated efforts of Stephan's group were to again provide a pivotal discovery. Combinations of Mes_3P and $E(C_6F_5)_3$ (E = B, Al) were found to react with tetrachloro-1,4-benzoquinone (p-$O_2C_6Cl_4$) through single electron transfer (SET) and with the production of the $[Mes_3P]^{\bullet+}$ radical cation, which was observable by electron paramagnetic resonance (EPR) spectroscopy.[7] Although this observation was rapidly augmented with further evidence of a radical-based FLP chemistry,[8,9] such exemplars remain some way from applicability.

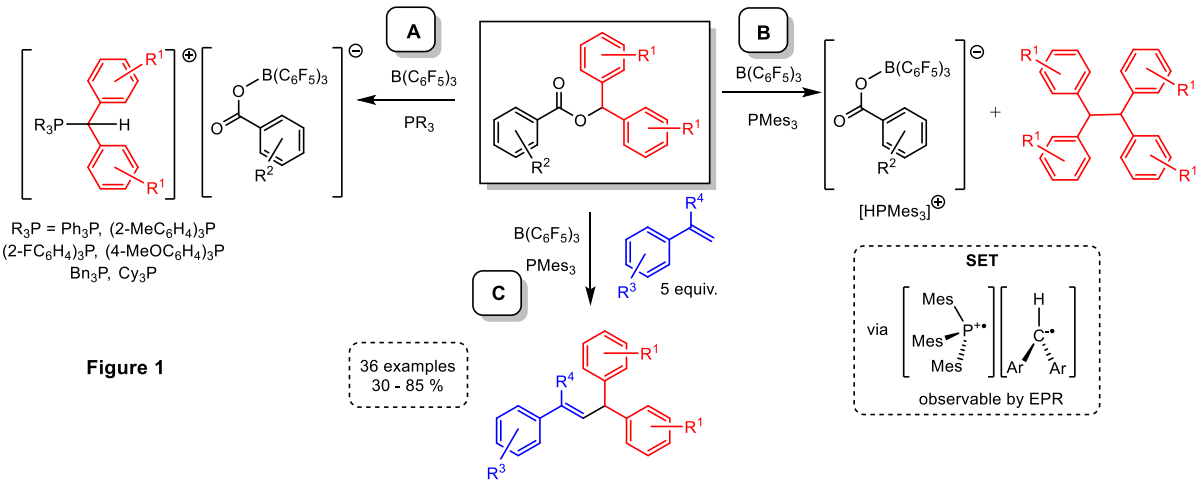

Figure 1

The work of Melen and co-workers reported in the February issue of CRPS brings this latent synthetic potential to fruition.[10] Combinations of the electrophilic borane, $B(C_6F_5)_3$, with a variety of Lewis basic trialkyl- and triarylphosphines are found to induce a C(sp^3)-O bond cleavage process when added to a fluoro-substituted benzhydryl ester derivative. A majority of these combinations yield the corresponding phosphonium-borate (Figure 1, path **A**). Although unusual, this outcome may be rationalised as 'typical' two electron FLP-induced behaviour. Significantly contrasting reactivity, however, is observed when the phosphine component is replaced by Mes_3P. Mild heating of this latter system induces a sequence of distinctive colour changes and the ultimate production of a phosphonium borate alongside homocoupling of the benzhydryl unit (Figure 1, path **B**). Evaluation of this reaction by EPR spectroscopy and DFT calculations provide the authors with convincing evidence that this contradivergent behaviour may be traced to the initial generation of the $[Mes_3P]^{\bullet+}/[CH(H)Ar_2]^{\bullet}$ radical ion pair, which is formed by SET.

While this observation is striking in itself, the authors further demonstrate that this reactivity may be exploited in a novel sp^2-sp^3 C-C heterocoupling process when the ester C-O activation is induced in the presence of a suitably-disposed styrene. These conditions enable the β-functionalisation of styrenes bearing both electron-donating and electron-withdrawing substitution and provide the *E*-isomer of the C-C coupled product (Figure 1, path **C**). The protocol is also be applicable to the functionalisation of mono- and 1,1-disubstituted styrenes and can be further generalised to the incorporation of 9*H*-fluorenyl and unsymmetrical ester-derived radicals bearing either cyclohexyl or methyl substitution.

While the current reaction encompasses a relatively narrow range of ester and alkene substrates, the broader significance of this work most likely lies in the increasing prominence of radical reactions in organic synthesis. Although these are obviously early days, an ability to achieve the bespoke generation of reactive free radicals, simply through judicious selection of the donor and acceptor energy level of a transition metal free system, is a compelling and potentially powerful concept. It is easy to foresee,

therefore, that these results could inspire researchers across many other areas, for example in radical-initiated polymerisation, where the controlled generation of free radicals is a primary consideration.

References

1. Stephan, D. W. (2016) The broadening reach of frustrated Lewis pair chemistry. *Science*, *354*, aaf7229.
2. Welch, G. C.; Juan, R. R. S.; Masuda, J. D.; Stephan, D. W. (2006) Reversible, metal-free hydrogen activation. *Science*, *314*, 1124.
3. Rokob, T. A.; Hamza, A.; Stirling, A.; Soós, T.; Pápai, I. (2008) Turning Frustration into Bond Activation: A
4. Theoretical Mechanistic Study on Heterolytic Hydrogen Splitting by Frustrated Lewis Pairs. *Angew. Chem. Int. Ed.*, *47*, 2435.
5. 4. Hamza, A.; Stirling, A.; Rokob, T. A.; Pápai, I. (2009) Mechanism of hydrogen activation by frustrated Lewis pairs: A molecular orbital approach. *Int. J. Quantum Chem.*, *109*, 2416.
6. 5. Grimme, S.; Kruse, H.; Goerigk, L.; Erker, G. (2010) The Mechanism of Dihydrogen Activation by Frustrated Lewis Pairs Revisited. *Angew. Chem. Int. Ed.*, *49*, 1402.
7. Liu, L. L.; Cao, L. L.; Shao, Y.; Ménard, G.; Stephan, D. W. (2017) A Radical Mechanism for Frustrated Lewis Pair Reactivity. *Chem*, *3*, 259.
8. Dong, Z.; Cramer, H. H.; Schmidtmann, M.; Paul, L. A.; Siewert, I.; Müller T. (2018) Evidence for a Single Electron Shift in a Lewis Acid–Base Reaction. *J. Am. Chem. Soc.*, *140*, 15419.
9. Merk, A.; Großekappenberg, H.; Schmidtmann, M.; Luecke, M.-P.; Lorent, C.; Driess, M.; Oestreich, M.; Klare, H. F. T.; Müller, T. (2018) Single-Electron Transfer Reactions in Frustrated and Conventional Silylium Ion/Phosphine Lewis Pairs. *Angew. Chem. Int. Ed.*, *57*, 15267.
10. PLACEHOLDER TO CITE MELEN PAPER